British Journal of Medicine & Medical Research
15(12): 1-7, 2016, Article no.BJMMR.24756
ISSN: 2231-0614, NLM ID: 101570965

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Hunter Syndrome

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/24756
Editor(s):
(1) Miles Weinberger, Department of Pediatrics, University of Iowa Cystic Fibrosis Center, USA.
(2) Chan Shen, Department of Biostatistics, MD Anderson Cancer Center, University of Texas, USA.
Reviewers:
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(3) Anonymous, INSA, Portugal.
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(5) Silvio Omar Macedo Prietsch, Federal University of Rio Grande, Brazil.
(6) Ramesh Bhat. Y, Kasturba Medical College, Manipal University, Manipal, India.
Complete Peer review History: http://sciencedomain.org/review-history/14739

Mini-review Article

Received 31st January 2016
Accepted 13th May 2016
Published 22nd May 2016

ABSTRACT

The mini review of Hunter syndrome aimed to explore etiology, incidence, clinical manifestations, diagnosis and treatment by reviewing recent literatures. Hunter syndrome (mucopolysaccharidosis II: MPS II) is a genetic lysosomal storage disease which is rare, It's caused by deficiency of the enzyme iduronate-2-sulfatase (I2S). Initial manifestations of Hunter syndrome are not present at birth, but often begin around ages of 2 to 4, which may include macrocephaly, thickened lips, facial features with typical coarseness like a prominent forehead, a nose with a flattened bridge, and an enlarged protruded tongue, cardiomyopathy, bone deformities, Mongolian spots over the buttocks and neurologic deficits. Hunter syndrome is commonly diagnosed by urine test for glycosaminoglycans (GAGs). Management of MPS II involves palliative treatment, or hematopoietic stem cell therapy (HSCT) which is more effective at an early stage than the enzyme replacement therapy (ERT) by Idursulfase. Intrathecal ERT is under clinical trial and fusion protein treatments, and gene therapy is under development.

Keywords: Hunter syndrome; mucopolysaccharidosis II; glycosaminoglycans; ERT; HSCT.

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1. INTRODUCTION

Mucopolysaccharidosis type II; Hunter syndrome is classified as one of mucopolysaccharide storage disease or one of lysosomal storage diseases (LSDs). Hunter syndrome is an X-linked genetic disorder is caused by mutation in the gene encoding (IDS; OMIM# 309900) on the chromosome Xq27.3-q28 [1]. Lack of the lysosomal enzyme iduronate-2-sulfatase (I2S) is an essential defect in MPS II [2]. This X-linked disorder has clinical heterogeneity. In addition, there is considerable heterogeneity in the molecular mechanisms underlying iduronate-2-sulfatase gene (IDS) (HGNC:5389) alteration. Most LSDs have clinical heterogeneity with the broad phenotype from early-onset childhood lethal disease to attenuated disease resulting in a near normal life expectancy [3].

In 1917, Charles A. Hunter described a disease of MPS II as a rare X-linked genetic disorder caused by lack of I2S, resulting in progressive accumulation of glycosaminoglycans (GAGs) in various tissues and cells. Patients with MPS II excrete excessive dermatan sulfate and heparin sulfate in urine which can be examined to help diagnosis of MPS II [4].

2. INCIDENCE AND PREVALENCE

Prevalence of LSDs in the Northern Portuguese population is (25 per 100 000 live births) [5] which is about (50 per 100 000 live births) in each of Netherlands [6], Czech [7], and Australia [8]. A study conducted by Sheth et al. [9] 2013 included 1,110 children, 387 (34.8%) were found to be affected by different storage disorders. Of these, 115 children (29.6%) were born to consanguineous parents. Glycolipid storage disorders were the most commonly diagnosed LSDs (48 %) in this study population, followed by MPS disorders (22%) and sulfatide degradation defect (MLD and Krabbe disease) in 14% of the patients.

3. CLINICAL MANIFESTIONS AND DIAGNOSIS

MPS II is a multi-organ disease and it has mild or severe symptoms. Patients with severe MPS II have disturbed intellectual function with fast disease progression [10]. Clinical manifestations include severe respiratory obstruction, abdominal wall hernias, nasal and ear discharge. Initial manifestations of Hunter syndrome do not appear at birth, but often begin around the ages of 2 to 4, which may include macrocephaly, thickened lips, facial features with typical coarseness like a prominent forehead, a nose with a flattened bridge, and an enlarged protruded tongue, cardiomyopathy, bone deformities, and neurologic deficits as shown in Fig. 1 which patients die in the second decade of life [11,12].

In most cases of MPS, the total urinary GAG (uGAG) level is elevated. Excess GAGs in the urine indicate the likely presence of an MPS, but it is not a definitive diagnostic test for Hunter syndrome. If uGAG analysis reveals elevated dermatan and heparan sulfates, the definitive biochemical diagnosis of Hunter syndrome can be established through blood enzyme testing. Enzyme assays should be performed to determine deficiency of I2S enzyme activity in plasma leukocytes or fibroblasts. Molecular genetic testing of the IDS gene may be useful, but it is not usually needed for diagnosis [12].

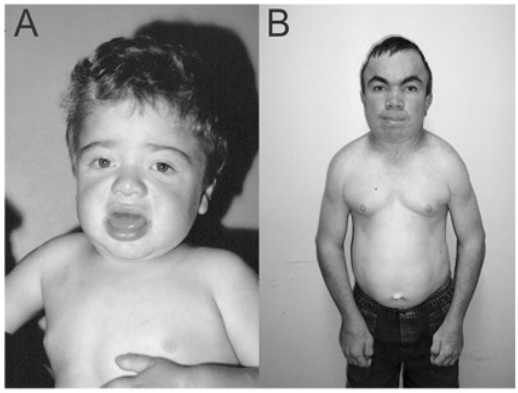

Fig. 1. Children with hunter's syndrome, A: Child with severe phenotype, B: Male adult with attenuated phenotype [12]

Lie [13] classified MPS II into two forms: A severe form (called MPS IIA as shown in Fig. 1: A) with progressive mental retardation and physical disability and death before age 15 years in most cases, and a mild form (called MPS IIB as shown in Fig. 1: B) compatible with survival to adulthood in which reproduction is known to have occurred [14], and in which intellect is impaired minimally. Wraith and others [1], stated that MPS II should be regarded as a continuum between two extremes (severe and attenuated).

Major signs and symptoms of MPS II are obstructive respiratory diseases, cardiac failure

due to valvar dysfunction, pulmonary hypertension and myocardial disease which are common causes of death. Patients with the more attenuated or who became adult usually have normal intelligence, but they may have progressive loss of vision caused by retinal dysfunction, spastic paresis caused by melon compression at the cranio-cerevical region, severe hip disease, cardiac and metachromatic cytoplasmic fibroblasts [1,15,16]. Sapadin and Friedman [17], noted extensive Mongolian spots over the buttocks, Para spinal area of the entire back and lumbar sacral area present at birth. Ochiai and others [18], investigated the occurrence of Mongolian spots in seven Japanese infants with MPS II before and after hematopoietic stem cell transplantation (HSCT) and results of their study indicated a strong clinical correlation between extensive Mongolian spots and MPS II in Asian population.

Yund and others [19], found significant association between somatic disease burden and white matter and corpus callosum volumes with attention deficits in patients with MPS II. Neither age at evaluation nor age at starting treatment predicted attention outcomes. Patients with complete deletion of the IDS locus often have atypical phenotypes, including ptosis, obstructive sleep apnea, and seizures [20,21]. Steen-Bondeson and others [22], suggested that some of these atypical features in MPS II patients may be caused by deletion of additional genes in the region of IDS.

In 2007 a clinical study conducted in Brazil [23], consisted of 77 patients with MPS II showed mean birth weight of patients was 3360 g, median age at onset of symptoms was 18 months and median age at diagnosis was 6 years with median age, 8.2 years; range, 2.8-53.0 years, those characterized with neurological degeneration, typical pebbly skin lesions, seizures and extensive dermal melanocytosis, and abnormal echocardiogram involved mitral valve regurgitation. In addition to presence of refraction errors, high urinary glycosaminoglycans, abnormal language development and mental retardation.

The mentioned above signs and symptoms may lead to the provisional diagnosis of MPS II which occurs from about 2 to 4 years of age. Additional evidence of MPS disorder is measuring the serum iduronate-2-sulfatase (I2S) enzyme activity, testing urine for GAGs, white blood cells, or fibroblasts from skin biopsy and analysis of the IDS gene can determine clinical severity. Prenatal diagnosis is depending on measuring IDS enzymatic activity in amniotic fluid or in chorionic villus tissue in 12th week of pregnancy [24,25].

Tonnesen and other [26], found that MPS II heterozygote is inhibited by fructose 1-phosphate or mannose 6-phosphate with specific technique. Petruschka and other [27], tested the Tonnesen's technique by studying various mixtures of normal and MPS II cells in culture as well as obligatory carriers. They concluded that the method 'seems to be suitable for carrier detection. Archer and other [28], concluded that carrier detection was best when hair-root analysis and serum enzyme levels were taken together. Daniele and Di Natale [29], demonstrated cross reacting material in the serum and fibroblasts of MPS II patients. Zlotogora and Bach [30], proposed that prenatal diagnosis of Hunter syndrome may be possible by measurement of iduronate sulfatase in the mother's serum. The level of IDS consistently rises in the serum of pregnant women. In pregnancies with MPS II -affected male fetuses, serum enzyme levels did not change. The normal increase occurs usually by the sixth to twelfth week of pregnancy.

Bakker and others [31], found that the IDS cDNA probe was partially deleted in 3 of 12 Dutch patients with MPS II. In 2 of the 3 patients, Southern blots showed the presence of a deletion junction fragment which could be used for highly reliable direct carrier detection in their families. Schroder and others [32], used different carrier detection tests, i.e., IDS activity in serum, sulfate incorporation in cultured skin fibroblasts, and RFLP analysis, in 13 unrelated families with 16 patients and 36 females at risk for MPS II. Twenty-nine females were confirmed as carriers, and in 5 women, the heterozygous state was excluded. The use of the intragenic IDS cDNA probes and flanking probes provided accuracy in carrier detection that was equal to or better than biochemical methods. Ben Simon-Schiff and others [33], confirmed the reliability of the serum assay of IDS activity in the identification of heterozygotes; the serum test correctly detected 11 of 12 of the first-degree relatives tested by the serum assay, 6 of 7 carriers, and 5 of 5 non-carriers. In a family in which there was no surviving affected individual, Timms and others [34], described carrier testing using direct dye primer sequencing of PCR products to identify mixed bases in an obligate carrier. Two mixed bases were observed within exon 8 of the IDS gene. These resulted in a missense mutation and

a nonsense mutation. Four additional female family members were screened for the same mutations, and none were found in any of these additional subjects, including one who had been identified previously as a carrier by skin biopsy. They concluded that this approach can be used to provide unambiguous information about a subject's carrier status, even in families in which the disorder is mild. As a means of molecular diagnosis, Jonsson and others [35], developed a rapid method to sequence the entire iduronate 2-sulfatase coding region: PCR amplicons representing the IDS cDNA were sequenced with an automatic machine, and output was analyzed by computer-assisted interpretation of tracings.

4. MANAGEMENT

Because of unique etiology of MPS II, management is very difficult. The treatment of MPS II disorder depends on each patient signs and symptoms, some of them requires an extensive palliative treatment to reduce the effects of the deterioration of body functions. Palliative strategies used include surgeries and therapies like bone marrow grafting or enzyme replacement therapy.

4.1 Hematopoietic Stem Cell Transplantation (HSCT)

Bone marrow grafting, or hematopoietic stem cell transplantation (HSCT) are treatment options for MPS II by providing a new source of the missing IDS. However, the results have been considered imperfect at best [36]. An alternative hematopoietic stem cell source for patients without a human leukocyte antigen-matched bone marrow. Alternatively, unrelated cord blood (UCB) is used the preferred donor source when HSCT is used to treat patients with LSD. HSCT delay progression of physical symptoms, and slow the cognitive deterioration, decrease mortality and alter complications such as graft-versus-host disease [37].

4.2 Enzyme Replacement Therapy

Enzyme replacement therapy (ERT) with recombinant human I2S (idursulfase) is used for treatment of patients with MPS II. Idursulfase is generated by recombinant DNA technology in a human cell line [37,38]. There have been reports that HSCT is more effective than conventional ERT but still indication of HSCT must be carefully considered with clinical stage, well-trained facility and staffs, age, and regimen [39-41] In addition, patients treated with idursulfase got improved liver and spleen volumes, left ventricular mass index, hearing and joints movement. Excretion of uGAG was also reduced, however, there is no significant change of respiratory function, eye, skeletal and CNS status. The risk of infusion appears to be greatest in the first six months of treatment [12,42]. Anaphylactic reactions, have the potential to be life threatening. Idursulfase is administered once per week as an intravenous (IV) infusion at a dose of 0.5 mg/kg [43]. As idursulfase does not cross the blood-brain barrier, so the challenges of treating the neurological features of MPS II remain [44].

4.3 Further Treatments

Researchers seeks to address the challenges of treating the neurological complications of Hunter syndrome, with focusing on developing well-tolerated therapies that can cross the blood-brain barrier [30]. Investigational experiments in animal models of LSDs, including Hunter syndrome, have shown that ERT with a different formulation of idursulfase to that used in conventional ERT delivered via the intrathecal route distributes throughout the CNS, penetrates brain tissue, and promotes clearance of lysosomal storage material [45]. In addition, analysis of splicing mutations in the IDS gene and the use of antisense oligonucleotides to exploit an alternative therapy for MPS II [46]. Finally, induced pluripotent stem cell (iPSC) technology, endows personalized medicine for future therapy without ethical issues and immunological rejection which embryonic stem cell (hES) treatment of many untreatable diseases in which Hunter syndrome is one of them [47].

5. CONCLUSION

MPS II represents a multisystem disorder which presents numerous clinical manifestations affecting most of the organs. Thorough examination and evaluation is required to classify the disorder into the exact type. The gold standard for diagnosis of MPS II in a male proband is deficient iduronate 2-sulfatase (I2S) enzyme activity in white cells, fibroblasts, or plasma in the presence of normal activity of at least one other sulfatase. Treatment options include hematopoietic stem cell transplantation (HSCT) or Enzyme replacement therapy (ERT).

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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